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and expression of AIB1. Alternatively, treatments may comprise contacting an AIB1 protein with molecule that specifically binds to the AIB1 molecule *in vivo*, thereby interfering with AIB1 binding with other factors such as p300 or CBP. Such processes are designed to inhibit signal transduction pathways involving AIB1, p300, CBP and other factors and therefore inhibit cancer cell proliferation that is effected via these pathways. As explained in more detail below, AIB1 overexpression results in increased ER-dependent transcriptional activity which confers a growth advantage upon AIB1 amplification-bearing clones during the development and progression of estrogen-dependent cancers.

Compounds which inhibit or disrupt the interaction of an AIB1 gene product with a steroid hormone receptor, e.g., ER, are useful as anti-neoplastic agents for the treatment of patients suffering from steroid hormone-responsive cancers such as breast cancer, ovarian cancer, prostate cancer, and colon cancer.

AIB1 polypeptides or peptide mimetics of such polypeptides, e.g., those containing domains which interact with steroid hormone receptors, can be administered to patients to block the interaction of endogenous intracellular AIB1 and a steroid hormone receptor, e.g., ER in an aberrantly proliferating cell. It is likely that AIB1 interacts with a wide range of human transcriptional factors and that regulation of such interactions will have important therapeutic applications.

Other features and advantages of the invention will be apparent from the following description of the preferred embodiments thereof, and from the claims.

SEQUENCE LISTING

The nucleic acid and amino acid sequences listed in the accompanying Sequence Listing are shown using standard letter abbreviations for nucleotide bases and three-letter code for amino acids. Only one strand of each nucleic acid sequence is shown, but the complementary strand is understood to be included by any reference to the displayed strand.

[SEQ. I.D. No. 1] SEQ ID NO:1 shows the nucleic acid sequence of the human AIB1 cDNA and the corresponding amino acid sequence.

[SEQ. I.D. No. 2] SEQ ID NO:2 shows the amino acid sequence of the Per/Arnt/Sim (PAS) domain of AIB1.

[SEQ. I.D. No. 3] SEQ ID NO:3 shows the amino acid sequence of the basic helix-loop-helix domain (bHLH) of AIB1.

[SEQ. I.D. No. 4] SEQ ID NO:4 shows the amino acid sequence of the human AIB1 protein.

[SEQ. I.D. No. 5] SEQ ID NO:5 shows the nucleic acid sequence of primer N8F1.

[SEQ. I.D. No. 6] SEQ ID NO:6 shows the nucleic acid sequence of the forward primer designed from the 5' sequence of pCMVSPORT-B11, PM-U2.

[SEQ. I.D. No. 7] SEQ ID NO:7 shows the nucleic acid sequence of the reverse primer designed from the 5' sequence of pCMVSPORT-B11, PM-U2.

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[SEQ. I.D. No. 8] SEQ ID NO:8 shows the amino acid sequence of the ER-interacting domain of AIB1.

[SEQ. I.D. No. 9] SEQ ID NO:9 shows the nucleic acid sequence of pCIP, the mouse ortholog of AIB1 and the amino acid sequence for this gene.

5 [SEQ. I.D. No. 10] SEQ ID NO:10 shows the nucleic acid sequence of the forward primer AIB1/mESTF1 used to screen mouse BAC.

[SEQ. I.D. No. 11] SEQ ID NO:11 shows the nucleic acid sequence of the reverse primer AIB1/mESTR1 used to screen mouse BAC.

10 [SEQ. I.D. No. 12] SEQ ID NO:12 shows the amino acid sequence of pCIP, the mouse ortholog of AIB1.

BRIEF DESCRIPTION OF THE DRAWINGS [FIGURES]

Fig. 1A is a diagram of an amino acid sequence of full length AIB1 (SEQ ID NO:4) in which residues highlighted in black are identical in AIB1, TIF2 and SRC1. Residues identical with
15 TIF2 (GenBank accession number X97674) or SRC-1 (GenBank accession number U59302) are highlighted in grey or boxed, respectively.

Fig. 1B is a diagram showing the structural features of AIB1. The following domains are indicated: bHLH domain, PAS domains (with the highly conserved PAS A and B regions shown in dark gray), S/T (serine/threonine)-rich regions, and a group of charged residues (+/-). A
20 glutamine-rich region and polyglutamine tract are also indicated. The numbers beneath the diagram indicate the location (approximate residue number) of the domain with respect to the amino acid sequence shown in Fig. 1A. The alignment was generated using DNASTAR software.

Fig. 2 is a photograph of a Northern blot analysis showing increased expression of AIB1 in the cell lines BT-474, ZR-75-1, MCF7, and BG-1.

25 Fig. 3 is a bar graph showing that the addition of full length AIB1 DNA to a cell resulted in an increase of estrogen-dependent transcription from an ER reporter plasmid. COS-1 cells were transiently transfected with 250 ng ER expression vector (pHEGO-hyg), 10 ng of luciferase reporter plasmid (pGL3.luc.3ERE or 10 ng pGL3 lacking ERE) and increasing amounts of pcDNA3.1-AIB1 and incubated in the absence (open bars) or presence of 10 nM 17 β -estradiol (E2, solid bars) or 100 nM 4-hydroxytamoxifen (hatched bars). Luciferase activity was expressed in
30 relative luminescence units (RLU). The data are the mean of three determinations from one of four replicate experiments. Error bars indicate one standard deviation.

Fig. 4 is a schematic diagram comparing the DNA and protein structures of pCIP (the mouse ortholog of AIB1) and the human AIB1; exons are shown as black boxes.

35 Fig. 5 is a table showing the introns and exons of the mouse AIB1 gene (pCIP). The "Exon" column refers to the number of the exon; "cDNA bp 5'-exon" refers to the nucleotide position in the mouse cDNA sequence for the 5' exon. "3' intron splice site" refers to the last few nucleotides of the 3' position of the intron. "Exon sequence" refers to the exon itself. "5' intron" refers to the adjacent intron reading from the exon into the splice donor dinucleotides (usually GT).

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Fig. 6 is a table showing the introns and exons of the human AIB1 gene (SEQ ID NO:1). The "Exon" column refers to the number of the exon; "cDNA bp 5'-exon" refers to the nucleotide position in the mouse cDNA sequence for the 5' exon. "3' intron splice cite" refers to the last few nucleotides of the 3' position of the intron. "Exon sequence" refers to the exon itself. "5' intron" refers to the adjacent intron reading from the exon into the splice donor nucleotides (usually GT).

DETAILED DESCRIPTION

The invention is based on the discovery of a novel gene, amplified in breast cancer-1 (AIB1), which is overexpressed in breast cancer. AIB1 has the structural features of a co-activator of the steroid hormone receptor family. The steroid hormone estrogen and other related steroid hormones act on cells through specific steroid receptors.

Members of the steroid receptor coactivator (SRC) family of transcriptional co-activators interact with nuclear hormone receptors to enhance ligand-dependent transcription. AIB1 is a novel member of the SRC family which was found to be overexpressed in breast cancers. The AIB1 gene is located at human chromosome 20q. High-level AIB1 amplification and overexpression were observed in several estrogen receptor (ER) positive breast and ovarian cancer cell lines, as well as in uncultured breast cancer specimens. AIB1 amplification is not confined to breast cancer but is also found in cancers of the lung, ovary, head and neck, colon, testicles, bladder, prostate, endometrium, kidney, stomach and also in pheochromocytoma, melanoma, ductal carcinoma and carcinoid tumor.

Transfection of AIB1 into cells resulted in marked enhancement of estrogen-dependent transcription. These observations indicated that AIB1 functions as a co-activator of steroid hormone receptors such as ER (including estrogen receptor α (ER α) and estrogen receptor β (ER β)), androgen receptor (e.g., expressed in prostate cells), retinoid receptor (e.g., isoforms α , γ , and retinoid X receptor (RXR)), progesterone receptor (e.g., expressed in breast cells), mineralocorticoid receptor (implicated in salt metabolism disorders), vitamin D receptor (implicated in calcium metabolism disorders), thyroid hormone receptor (e.g., thyroid hormone receptor α), or glucocorticoid receptor (e.g., expressed in spleen and thymus cells). The altered expression of AIB1 contributes to the initiation and progression of steroid hormone-responsive cancers by increasing the transcriptional activity of the steroid receptor.

A substantially pure DNA which includes an AIB1-encoding polynucleotides (or the complement thereof) is claimed. By "substantially pure DNA" is meant DNA that is free of the genes which, in the naturally-occurring genome of the organism from which the DNA of the invention is derived, flank the AIB1 gene. The term therefore includes, for example, a recombinant DNA which is incorporated into a vector, into an autonomously replicating plasmid or virus, or into the genomic DNA of a prokaryote or eukaryote at a site other than its natural site; or which exists as a separate molecule (e.g., a cDNA or a genomic or cDNA fragment produced by PCR or restriction endonuclease digestion) independent of other sequences. It also includes a